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IN THE U.S. PATENT AND TRADEMARK OFFICE

Inventor	Gabor BOGYE
Patent App.	09/890,029 (US Nat'l phase of PCT/HU00/00009)
Filed	24 July 2001
For	PHARMACEUTICAL COMBINATION OF PROGESTERONE AND FOLIC ACID
Art Unit	Not known

Hon. Commissioner of Patents
Washington, DC 20231

OIPE JC132
JAN 02 2002
PATENT & TRADEMARK OFFICE

INFORMATION DISCLOSURE STATEMENT

NOW COMES Applicant and files this Information Disclosure Statement Under 37 CFR 1.97.

The Information Disclosure Statement includes the following documents:

(1) Hungarian Patent Office Search Report dated 15 December 1999 (English translation);

(2) International Search Report done by the European Patent Office on 9 June 2000;

(3) Written Opinion rendered by the European Patent Office and dated 7 December 2000;

(4) Applicant's reply to the Written Opinion, said reply dated 6 March 2001;

(5) an International Preliminary Examination Report rendered by the European Patent Office and dated 10 May 2001; and

(6) a series of twelve prior art references that were either cited in the Hungarian Patent Office Search Report, in the

European Search Report or in the European Preliminary Examination Report, or which became known to Applicant as related prior art:

D1: JOURNAL OF WOMEN'S HEALTH AND GENDER-BASED MEDICINE, 1999, 8/9, Pages 1167-1172;

D2: GB 2 131 292;

D3: JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION, vol. 2, no. 3, 1983, pages 221-230, ISSN: 0731-5724;

D4: AMERICAN JOURNAL OF CLINICAL NUTRITION, vol. 35, no. 1, January 1982, pages 73-82;

D5: THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, vol. 226, no. 12, 17 December 1973, pages 1421-1424, ISSN: 0098-7484;

D6: JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, vol. 277, no. 22, June 1997, pages 1775-1781;

D7: NEW ENGLAND JOURNAL OF MEDICINE, vol. 334, March 1996, no. 12, pages 759-762;

D8: AMERICAN JOURNAL OF CLINICAL NUTRITION, vol. 65, no. 2, February 1997, pages 572-573;

D9: SCAND J CLIN LAB INVEST 1992; 52: pages 283-287;

D10: NEW ENGLAND JOURNAL OF MEDICINE, vol. 338, no. 15, 1998, Pages 1042-1050;

D11: FORTSCHR NEUROL PSYCHIATR 1996 JUL; 64(7): Pages 271 -277 (abstract); and

D12: Ann Epidemiol 1997 May ;7(4) pages 285-293.

None of these references taken alone or in combination is believed to provide any basis to reject any claim now presented as either anticipated under 35 USC 102 or as obvious under 35 USC 103.

Applicant has discovered a method of treating a patient to reduce an elevated plasma homocysteine content resulting from taking a gestagen hormone composition thereby reducing a risk of thromboembolism induced by taking the gestagen hormone, which comprises the step of administering to the woman patient simultaneously, previously or subsequently to taking the gestagen hormone composition a therapeutic amount of a compound selected from the group consisting of folic acid, Vitamin B_6, Vitamin B_{12}, betaine, choline, acetylcysteine, or a metabolic precursor thereof, in an amount effective to reduce the elevated plasma homocysteine content resulting from taking the gestagen hormone composition. Applicant's investigations have shown that homocysteine content in the blood plasma of patients undergoing gestagen therapy increases when gestagens are administered <u>without any influence on the levels of folic acid in the blood</u>.

In Examples c and e in the present application, Applicant demonstrates reduction of homocysteine levels in the blood of patients with hyperhomocysteineaemia (HCY) caused by administration of gestagens. The reduction in blood levels of homocysteine is achieved by administering to the patient either folic acid or Vitamin B_6 according to the present invention.

The extent of reduction of HCY in these patients according to Example c was 69% and according to Example e was 65%

employing folic acid therapy together with the gestagen in comparison to homocysteine levels in a control group of patients who were administered only gestagen. These levels of reduction of HCY are much greater than the levels of reduction of HCY found in the prior art where patients having a folic acid deficiency and resulting elevated levels of homocysteine were administered folic acid. Then the level of HCY reduction was only 45 to 50% lower than that levels for a control group of patients who were not admibnistered folic acid. See page 5, lines 15 to 25 of the application. It is emphasized that the 45 to 50% reduction of HCY levels disclosed in the prior art related to the treatment of patients whose high blood level of HCY had causes which had nothing to do with the administration of gestagens. In the prior art study of reducing HCY levels, the patients' HCY was caused by a genetic folic acid deficiency having nothing to do with administration of gestagens.

Applicant concludes based upon the data obtained in Examples a through e in the present application that folic acid, Vitamin B_6 and the other B Vitamins employed according to the presently claimed method of treatment possess a protective activity against an increase in the homocysteine level in the blood caused by administration of gestagens through a biochemical mechanism that is far different and far more complex than merely blocking the activity of the gestagens to cause a folic acid deficiency. There is no suggestion in any of the cited prior art of record that folic acid, Vitamin B_6 or any of the other B Vitamins administered

according to the present invention could so effectively prevent the development of HCY in patients undergoing treatment with gestagens.

In the Written Opinion of the European Patent Office dated 12 December 2000 the European Examiner indicated his belief that the combination of the (D5) JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 1973 reference and the (D7) NEW ENGLAND JOURNAL OF MEDICINE 1996 reference rendered the claims to a method of treatment to reduce homocysteine levels in a female patient by administering folic acid or other B Vitamins obvious.

Applicant strongly traversed this rejection. In a communication dated 6 March 2001 Applicant pointed out to the European Examiner that the D5 reference included administration of gestagen oral contraceptives to women in conjunction with folic acid to treat abnormal growth of cervicovaginal cells. In this study only 17 to 21% of the female patients had abnormally low folic acid concentration in the blood at the beginning of the treatment. Thus the overwhelming majority of these female patients did not have any deficiency in the concentration of folic acid in the plasma. Furthermore there is no mention or suggestion in this reference to administer folic acid or any other B Vitamin in conjunction with a gestagen for the purpose of lowering the blood level of homocysteine elevated as a result of administration of the gestagen. There is furthermore no recognition in this reference that administration of gestagens to a patient will increase the blood levels of homocysteine.

The D7 reference discloses that elevated plasma levels of HCY are a risk factor in deep vein thrombosis. The reference discloses on page 762 that folic acid, Vitamin B_6 and Vitamin B_{12} may be determined through future experimentation to be effective in reducing high levels of HCY. However, there is no mention or suggestion in this reference of administering folic acid, Vitamin B_6 or Vitamin B_{12} in conjunction with gestagens to a patient taking gestogens in order to reduce elevated levels of HCY caused by administration of the gestagen. In such a situation the patient does not necessarily have a deficiency in the level of folic acid in the blood. Nor is there any suggestion in the combination of References D5 and D7 to administer to a female patient undergoing treatment with gestagens, an amount of folic acid, Vitamin B_6 or Vitamin B_{12} effective to lower the amount of HCY in the plasma thereby removing the risk of thrombosis in the patient.

Applicant also pointed out that according to Examples c and e the extent of reduction of homocysteine levels in the blood by employing folic acid therapy in combination with a gestagen was surprisingly high at 69% and 65% respectively over the homocysteine levels obtained where only the gestagen was administered to patients serving as a control group. These levels of reduction of HCY are much greater than the levels of reduction of HCY found in the prior art treatment of patients with elevated levels of homocysteine with folic acid where the level of reduction was only 45 to 50% respectively over the homocysteine levels obtained where the

folic acid was not administered to patients serving as a control group.

In the International Preliminary Examination Report dated 14 May 2001 the European Examiner indicated that he now agreed with the Applicant and that the present invention did indeed possess an inventive step not found in the combination of References D5 and D7. In Part 6 of the second International Preliminary Examination Report the European Examiner noted that only 17 to 21% of the women taking oral contraceptives (OCAs) had a decreased serum foliate concentration. The European Examiner agreed that it was not possible, on the basis of the combination of references D5 and D7 to conclude that administration of gestagen type hormones to a patient systematically leads to subnormal blood levels of folic acid and consequently to elevated plasma homocysteine levels, which are responsible for an increased risk of thromboses. The European Examiner also noted that most of the patients treated by the presently claimed method with folic acid or the other specified B Vitamins to reduce levels of homocysteine did not have any blood level deficiency in folic acid and that there is no evidence in patients taking gestogens of any relationship between an elevated plasma homocysteine level and the level of folic acid in the blood.

Applicant believes that no combination or subcombination of the cited prior art references provides any basis to reject any claim now presented as obvious under 35 USC 103.

Favorable action in this case is earnestly solicited.

Respectfully submitted,
The Firm of Karl F. Ross P.C.

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Enclosures: PTO 1449
References

FORM PTO-1449 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

LIST OF PATENTS AND PUBLICATIONS

ATTY DOCKET NO.	SERIAL NO.
21965	09/890,029
APPLICANT	
Gabor BOGYE	
FILING DATE	GROUP
24 July 2001	

U.S. PATENT DOCUMENTS

EX. INIT		DOCUMENT NO. Cntry code - No.	DATE MM-YYYY	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	AA	US-					
	BB	US-					
	CC	US-					
	DD	US-					

FOREIGN PATENT DOCUMENTS

		DOCUMENT NO. Cntry Code - No.	DATE MM-YYYY	COUNTRY	NAME	CLASS	TRANSL. YES	TRANSL. NO
	AE	GB 2 131 292	1 DEC. 1982	GREAT BRITAIN	C.H. MORTIMER			
	AF							

OTHER ART (Including Author, Title, Date, Pertinent Pages, Etc.)

	AG	Journal of Women's Health; XP 000913564; V.M. BARNABEL et al; PLASMA HOMOCYSTEINE IN WOMEN TAKING ...
	AH	Journal of the American College; XP 002114784; B.M. RHODE et al; EFFECT OF ORANGE JUICE, FOLIC ...
	AI	American Journal of Clinical Nutrition; XP 002114785; C.E. BUTTERWORTH et al; IMPROVEMENT IN CERVICAL ...
	AJ	Journal of American Medical Association; XP 002114786; N. WHITEHEAD et al; MEGALOBLASTIC CHANGES IN THE ...
	AK	Journal of American Medical Association; I.M. GRAHAM; PLASMA HOMOCYSTEINE AS A RISK FACTOR ...
	AL	The New England Journal of Medicine; M.D. HEIJER et al; HYPERHOMOCYSTEINEMIA AS A RISK FACTOR ...
	AM	American Journal of Clinical Nutrition; V. HERBERT et al; CALL FOR ENDORSEMENT OF A PETITION TO FDA ...
	AN	Scand J Clin Lab Invest; L. BRATTSTROM et al; PLASMA HYMOCYSTEINE IN WOMEN ON ORAL OESTROGEN ...
	AO	The New England Journal of Medicine; F.H. EPSTEIN; HOMOCYSTEINE AND ATHEROTHROMBOSIS
	AP	Fortschr Neurol Psychiatr 1996 Jul;64(7):271-7; W. LALOUSCHEK et al; HYPERHOMOCYSTEINEMIA - AN INDEPENDENT ..
	AQ	Ann Epidemiol 1997 May;7(4):285-93; T. SHIMAKAWA et al; VITAMIN INTAKE: A POSSIBLE DETERMINANT OF ...
	AR	

EXAMINER	DATE CONSIDERED

EXAMINER: Initial if Reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

28 December 2001

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